

IgE-Mediated Adverse
Reactions to Vaccines
Workshop 4804
San Antonio February 25, 2013

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Faculty Disclosure Information

- I have not had a significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.
- This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA, but will include some discussion of non-FDA approved skin test materials.

Objectives

- Develop a diagnostic approach to the evaluation IgE-mediated reactions to vaccines
- Provide advice regarding the future administration of vaccines
- Safely administer influenza vaccine to egg-allergic recipients

**Adverse reactions to vaccines
practice parameter 2012
update.**

**Kelso JM, Greenhawt MJ, Li
JT, et al.**

**Journal of Allergy and Clinical
Immunology 2012; 130:25-43.**

Summary Statement 5. All suspected anaphylactic reactions to vaccines should ideally be evaluated in an attempt to determine the culprit allergen.

- When a patient experiences an apparently IgE-mediated reaction after an immunization, often labeled “allergic” and advised against future doses
- This approach should be avoided because it may leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite their allergy.
- In addition, not knowing the constituent of a vaccine to which the patient is allergic may pose a risk with future vaccinations that contain the same ingredient.

Summary Statement 6. IgE-mediated reactions to vaccines are more often caused by vaccine components such as gelatin, rather than the immunizing agent itself.

Gelatin

- Gelatin is added to many vaccines as a stabilizer
- Gelatin in vaccines is bovine or porcine, which are extensively cross-reactive
- Responsible for many anaphylactic reactions to MMR, varicella, and (the old) Japanese encephalitis vaccines.
- A history of allergy to the *ingestion* of gelatin should be sought before the giving a gelatin-containing vaccine; negative history may not exclude an allergic reaction to gelatin *injected* with the vaccine.

- Persons who react to gelatin on ingestion should be evaluated by an allergist prior to administration of gelatin-containing vaccines.
- If the history is consistent with an immediate-type allergic reaction to gelatin confirmed by skin tests or serum specific IgE, skin test with vaccines prior to administration.
 - If negative, give in usual manner but observe for 30 minutes afterward.
 - If positive, give vaccine in graded doses

Gelatin Content of Vaccines 2013

Vaccine	Gelatin Content
Influenza (Fluzone, Sanofi Pasteur)	250 micrograms per 0.5 ml dose
Influenza (FluMist, MedImmune Vaccines, Gaithersburg, Maryland)	2000 micrograms per 0.2 ml dose
Measles, Mumps, Rubella (MMRII, Merck, Whitehouse Station, New Jersey)	14,500 micrograms per 0.5 ml dose
Measles, Mumps, Rubella, Varicella (ProQuad, Merck)	11,000 micrograms per 0.5 ml dose
Rabies (RabAvert, Novartis, Emeryville, California)	12,000 micrograms per 1.0 ml dose
Typhoid Vaccine Live Oral Ty21a (VIVOTIF, Berna, Coral Gables, Florida)	capsule
Varicella (VARIVAX, Merck)	12,500 micrograms per 0.5 ml dose
Yellow Fever (YF-VAX, Sanofi Pasteur)	7,500 micrograms per 0.5 ml dose
Zoster (ZOSTAVAX, Merck)	15,580 micrograms per 0.65 ml dose

Egg

- Measles and mumps vaccines and one type of rabies vaccine are grown in chick embryo fibroblast cultures and contain negligible or no egg protein
- Thus, MMR can be administered to egg allergic children without skin testing and without adverse reactions
- Egg protein is present in higher amounts in influenza and yellow fever vaccines and could *in theory* cause reactions in egg allergic patients.

Influenza vaccine contains measurable quantities of egg protein (ovalbumin); does this cause systemic reactions when injected into egg-allergic patients?

- 28 published studies involving >4300 egg-allergic subjects getting influenza vaccine without *any* serious reactions (no respiratory distress or hypotension), and with only a low rate of minor reactions (hives, mild wheezing).
- So, the answer appears to be no.

But what about patients with severe egg allergy?

- Most studies have specifically *included* patients with histories of severe anaphylaxis (n = 656) with egg ingestion and these patients also tolerate the vaccine.
- So, even these patients do not appear to be at risk of serious reaction.

Why are there no serious reactions being reported?

- 3/4 manufacturers of injectable trivalent influenza vaccine (TIV) report the maximum amount of ovalbumin in the package insert and the other will provide the information on request.
- The claimed amounts are all < 1 mcg per 0.5 mL dose.
- The measured amounts in independent laboratories are usually much lower than the claimed amounts.

What about LAIV?

- Although the intranasally-administered live attenuated influenza vaccine (LAIV) contains a low amount of ovalbumin, all published studies to date have evaluated the injectable trivalent inactivated vaccine (TIV), and thus TIV rather than LAIV should be used for egg-allergic recipients.

What about cell culture derived TIV?

- A cell culture based influenza vaccine that does not contain any egg protein was approved by the FDA in November of 2012 for use in patients 18 years of age and older.

What about cell culture derived TIV?

- If readily available, this vaccine would be preferred in egg-allergic adults. However, the opportunity to immunize an egg-allergic adult should not be missed if the cell culture-based vaccine is not readily available, in which case such patients should receive egg-based vaccine.

What about cell culture derived TIV?

- Studies of this vaccine in children are underway, however until they are completed, the vaccine should not be used in patients under age 18 because some influenza vaccines have been found to be less immunogenic in certain age groups and others have been found to have higher rates of adverse reactions in certain age groups, and the risk of the egg-based vaccines in egg-allergic patients is minimal.

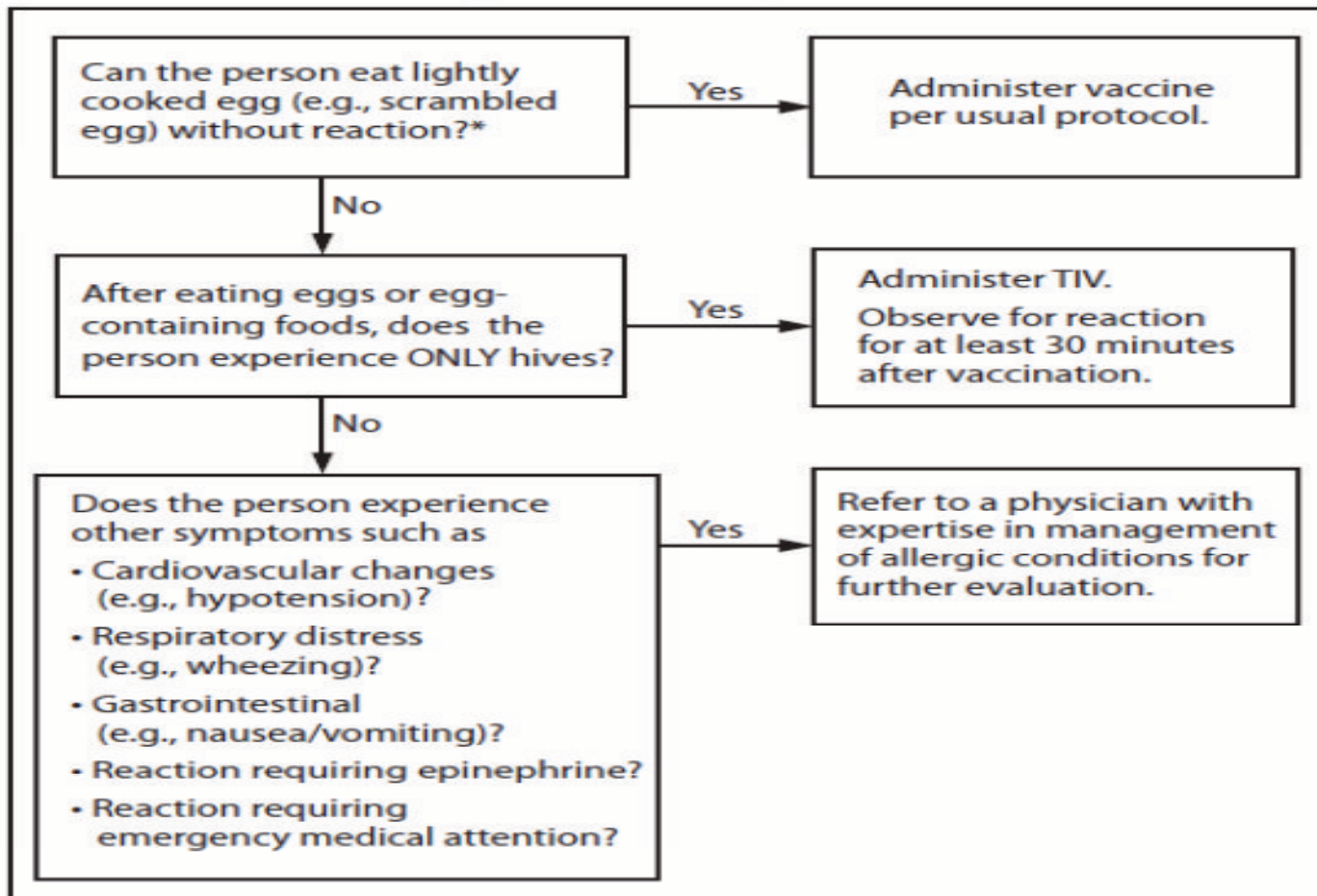
Ovalbumin content of injectable trivalent Influenza vaccines (TIV) approved for the 2012-13 season

Brand name	Manufacturer	Approved ages	Ovalbumin content (mcg per 0.5 mL dose *)†
Afluria	CSL Biotherapies (Merck)	≥ 9 years	≤ 1
Agriflu	Novartis	≥ 18 years	≤ 0.4
Fluarix	GlaxoSmithKline	≥ 3 years	≤ 0.05
Flucelvax	Novartis	≥ 18 years	0
FluLaval	ID Biomedical Corporation of Quebec (GlaxoSmithKline)	≥ 18 years	≤ 1
Fluvirin	Novartis	≥ 4 years	≤ 1
Fluzone	Sanofi Pasteur	≥ 6 months	~0.1
Fluzone High-Dose	Sanofi Pasteur	≥ 65 years	~0.1

*Dose 0.25 mL 6-35 months, 0.5 mL ≥ 3 years

† Information in package inserts except Fluzone and Fluzone High-Dose from Sanofi Pasteur by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com)

FIGURE 2. Recommendations regarding influenza vaccination for persons who report allergy to eggs — Advisory Committee on Immunization Practices, United States, 2012–13 influenza season



Abbreviation: TIV = trivalent inactivated vaccine.

* Persons with egg allergy might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy.

“Other measures, such as dividing and administering the vaccine by a two-step approach and skin testing with vaccine, are not necessary”

Yellow Fever Vaccine

- A history of allergy after the ingestion of egg should be sought prior to the administration of yellow fever vaccine
- Persons with positive histories should be skin tested with yellow fever vaccine prior to administration
 - If negative, give in usual manner but observe for 30 minutes afterward.
 - If positive, give vaccine in graded doses

Yeast

- Hepatitis B vaccines are grown in *Saccharomyces cerevisiae* (baker's yeast or brewer's yeast) and contain residual yeast protein
- However, adverse reactions to these, if any, appear to be rare
- Human papillomavirus vaccine may also contain residual yeast protein

- Yeast allergy itself is very rare but, if a patient has a history of clinical reactivity to Baker's or Brewer's yeast and a positive skin test to *Saccharomyces cerevisiae*, skin test them with yeast-containing vaccines prior to administration.
 - If negative, give in usual manner but observe for 30 minutes afterward.
 - If positive, give vaccine in graded doses

Latex

- The “rubber” in vaccine vial stoppers or syringe plungers may be dry natural rubber (DNR) latex or synthetic rubber.
- Those made with DNR pose a theoretical risk to the latex allergic
- A review of > 160,000 VAERS reports found only 28 cases of possible immediate-type allergic reactions after receiving a DNR-containing vaccine, and these may have been due to other components

- Latex content of vaccine packaging is provided is updated at:
<http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf>

- Patients with latex allergy can safely receive vaccines from vials with non-DNR stoppers.
- If the only available preparation has a latex stopper, the stopper should be removed and the vaccine drawn up directly from the vial without passing the needle through the stopper.
- If the only available vaccine contains latex in the packaging that cannot be avoided, such as in a prefilled syringe, the vaccine can still be administered but the patient should be observed for at least 30 minutes afterward.

Suggested approach to patients with allergy to vaccine components.

If positive skin test or serum specific IgE antibody to allergen	Vaccine	Vaccine skin testing prior to administration*	30 minute observation period after vaccination
Gelatin	See table	Yes	Yes
Egg	Influenza	No	Yes
	Yellow fever	Yes	Yes
Yeast	Hepatitis B	Yes	Yes
	HPV4	Yes	Yes
Latex	http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf .	No	Yes

* If positive, consider administration in graded doses.

Summary Statement 7. Patients who have had an apparent anaphylactic reaction after immunization should undergo immediate-type allergy skin testing to help confirm that the reaction was IgE-mediated and determine the responsible component of the vaccine.

- To determine whether a vaccine was responsible for an apparent allergic reaction, skin test with the vaccine
 - first by prick method (full-strength unless history truly life-threatening)
 - If negative, ID 1:100
- As with any (especially non-standardized) skin test reagent, false positive (irritant) and clinically irrelevant positive results may occur
- Likewise, false-negatives also possible

- If the suspect vaccine contains gelatin, egg, latex or yeast, skin test for these
- Egg and yeast extracts commercially available
- Gelatin (not FDA-approved): dissolve 1 teaspoon (5 g) of any sugared gelatin powder (e.g., Jell-O) in 5 mL of NS to create a prick skin test solution
- Latex (not FDA-approved): soak 2 fingers of latex glove or a toy balloon in 5 mL of NS to create a prick skin test solution
- In vitro assays for specific IgE antibody commercially available for gelatin, egg, latex and yeast

Summary Statement 8. If the intradermal skin test result is negative, the chance that the patient has IgE antibody to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. It is prudent nonetheless, in a patient with a history suggestive of an anaphylactic reaction, to administer the vaccine under observation with epinephrine and other treatment available.

- No formal studies to evaluate the positive and negative predictive values for vaccine skin tests
- Dilutions of vaccines of 1:100 have been demonstrated to be nonirritating for intradermal testing
- No reports of patients with negative intradermal skin test reacting to subsequent administration of vaccine

Summary Statement 9. In patients with histories and skin test results consistent with an IgE-mediated reaction to a vaccine, who require additional doses of the suspect vaccine or other vaccines with common ingredients, consideration can be given to administering the vaccine in graded doses under observation.

- If vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses

Administration of Vaccines in Graded Doses

For a vaccine for which the full normal-dose volume is 0.5 mL,
give the following doses at 15-minute intervals as tolerated

0.05 mL, 1:10 dilution

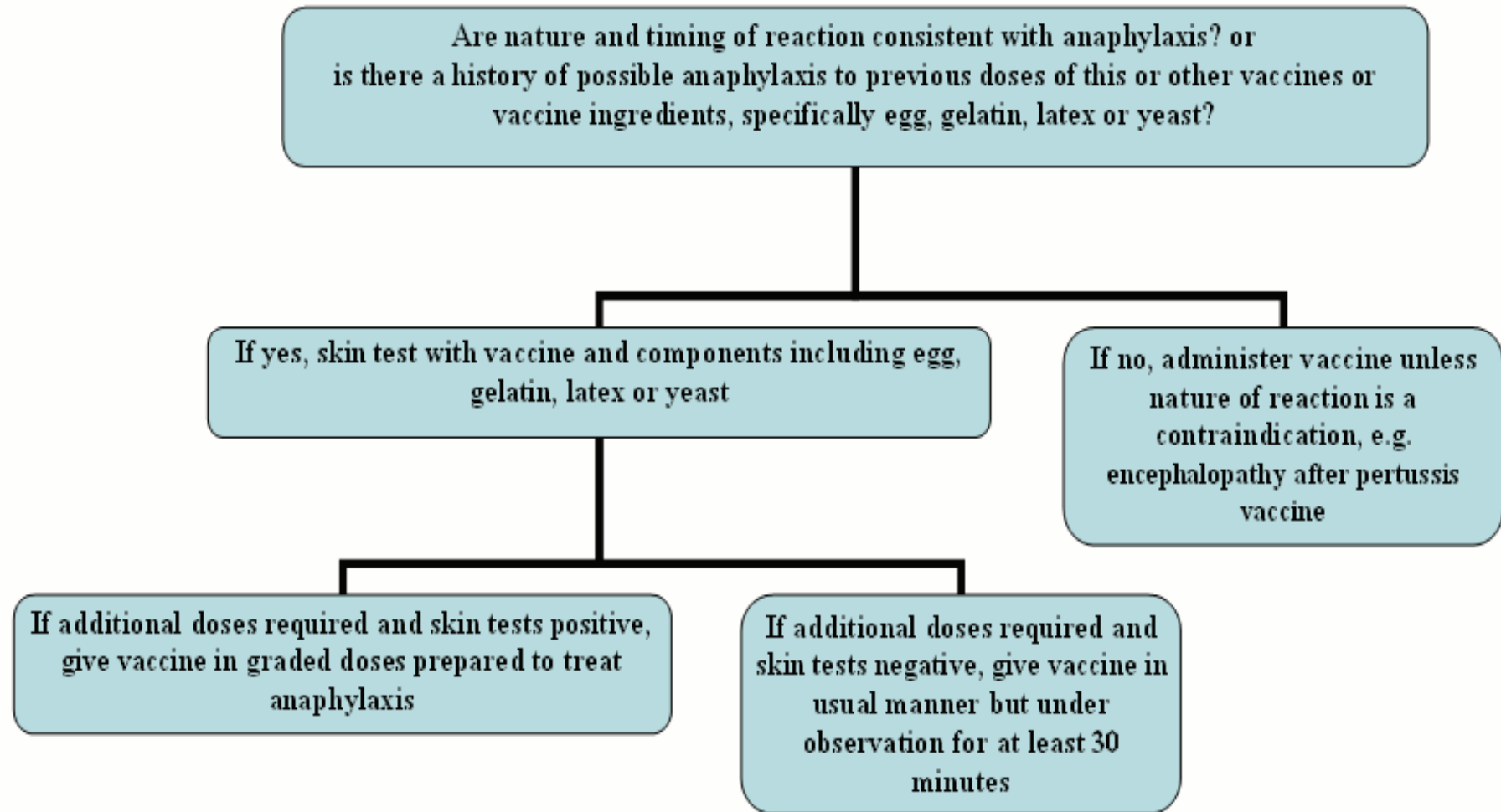
0.05 mL, full strength

0.1 mL, full strength

0.15 mL, full strength

0.2 mL, full strength

Suggested approach to suspected adverse reaction to a vaccine



Summary

- Patients with suspected allergy to vaccines or vaccine components should be evaluated by an allergist
- Most patients with suspected allergy to vaccines can receive vaccination safely